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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/753,851	12/02/96	WEINBERG	J 1579-21

EXAMINER

HM12/0908

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ART UNIT	PAPER NUMBER
1644	50

DATE MAILED: 09/08/99

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 9/23/98 and 4/2/99

☑ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 8-12, 14-19, 23-25 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 8-12, 14-19, 23-25 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

1. Applicant's amendment, filed 9/23/98 (Paper No. 48), is acknowledged.
Claim 25 was added.

Applicant's amendment, filed 4/2/99 (Paper No. 49), is acknowledged.
Claims 21-22 have been canceled.
Claim 10 has been amended.

Claims 1-7 and 13 have been canceled previously.
Claim 20 was not entered.
It is noted that claim 25 was added to replace previously unentered claim 20.
Claims 8-12 and 14-19 and 23-25 are pending.

2. The text of those sections of Title 35 USC not included in this Action can be found in prior Actions.
The rejections of record can be found in previous Office Actions (Paper No. 16/22/34/38/41/46).

As pointed out previously that the instant claims are free of the prior art, this Office Action will be considering both previously elected and nonelected species encompassing anti-CD44 antibodies, soluble CD44, CD44 oligopeptides and hyaluronate

Therefore, claims 8-12, 14-19 and 23-25 are under consideration.

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821-1.825, however, this application fails to comply with the requirements for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

Applicant is required to fulfill these requirements by defining the SEQ ID NOS in both the specification and claims.

The following procedure is to be used for cases that contain the same sequence disclosure as the parent. The applicant need not submit a new computer readable from of the Sequence Listing in this rule 60 continuation. However, (1) the specification must contain a paper copy of the Sequence Listing, (2) applicant must request in writing that the CRF in the parent case be used to prepare a file for the offspring and (3) applicant must submit a statement that the paper copy of the Sequence Listing in the offspring is identical to the computer readable form submitted in the parent case.

4. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84.
Please see the form PTO-948 previously sent in Paper No. 26.
Applicant is reminded to change the Brief Description of the Drawings in accordance with these changes.

5. The previous rejection under 35 U.S.C. § 112, first paragraph, written description (new matter) has been obviated by the cancellation of claims 21-22.

6. Claims 8-12 and 14-19 and 23-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention essentially for the reasons of record set forth in Paper No. 46.

Applicant's arguments, filed 4/2/99 (Paper No. 49), have been fully considered but are not found convincing.

In contrast to applicant's assertions, the skilled artisan as well as the rejection of record were well aware of the lack of correlation or predictability between in vitro and animal models and methods of reducing or inhibiting HIV infection, particularly in vivo at the time the invention was made.

In contrast to applicant's assertions, the examiner does not require 100% efficacy to meet the 112, first paragraph, enablement requirements. Rather, it has been noted that both the examiner and the applicant have agreed that the instant application has demonstrated the ability of CD44-specific antibodies to inhibit HIV infection of mononuclear phagocytes in vitro under defined conditions. However, the examiner and the applicant have disagreed whether this would be predictive of the ability of CD44-specific antibodies to inhibit HIV infection of any susceptible cell in vitro and in vivo, encompassed by the claimed methods. The rejection of record has not been based upon an issue of 100% effectiveness, as argued by applicant.

In contrast to applicant's reliance on Ueno et al. (U.S. Patent No. 4,840,941) to support the instant methods; the following of record is noted. While there may some evidence that CD44-specific agents including CD44-specific antibodies/peptides and hyaluronic acid/hyaluronate can inhibit HIV infection and expression under in vitro conditions; there is insufficient evidence that the mechanism of action operates via CD4-facilitated entry of HIV into cells. For example, Ueno et al. (U.S. Patent No. 4,840,941) discloses the criticality of sulfate groups in the inhibition of HIV infectivity and reverse transcriptase activity (see entire document, particularly Example 9).

Applicant's arguments concerning credibility or utility under 35 USC 101 are acknowledged; hoever the rejection is made under 35 USC 112, first paragraph, enablement.

With respect to the lack of consistency between applicant's assertions of record and observations; the following is reiterated in response to applicant's arguments and reliance of record on targeting CD44 on monocytes to reduce or prevent HIV infection, as encompassed by the claimed methods.

It has been well known in the art that cellular CD4 has been recognized as the predominant membrane protein that interacts with HIV. However, it has been well known that HIV infection occurs in cells that express variable or no detectable levels of CD4. It has been well known that $CD4^+$ T cells are the primary target of HIV infection both in vitro and in vivo. Therefore, it would not have been predictable that targeting CD44 in mononuclear phagocytes would affect HIV infection of any susceptible cell either in vitro or in vivo. For example, either the individual or the blood would be infected by HIV via CD4, irregardless of blocking CD44 infectivity of mononuclear phagocytes. Further, it is noted that

CD44-specific antibodies can block HIV infection of mononuclear phagocytes in vitro, however these same antibodies can not block the infection of mitogen-stimulated lymphocytes or cells of a T lymphocyte line in vitro (Rivadeneira et al., Aids Research and Human Retroviruses, 1995; see entire document including Abstract; of record). Therefore applicant's assertions of record have not appeared consistent with applicant's own observations

Applicant has not disclosed how to use CD44-specific antibodies, soluble CD44, CD44 oligopeptides and hyaluronate to inhibit HIV infection or to inhibit CD44-facilitated HIV infection therapeutically in humans. There is insufficient information or nexus of the invention with respect to the in vitro or in vivo ability of claimed therapeutic strategies to inhibit HIV infection or to inhibit CD44-facilitated entry of HIV into cells in vivo or into monocytic cells in vitro in a mixed cell population. In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of biopharmaceutical drugs such as antibodies can be species- and model-dependent, it is not clear that reliance on the in vitro inhibition of monocyte infection by a particular HIV strain (Example on page 31 of the instant specification) accurately reflects the relative efficacy of the claimed therapeutic strategies, which broadly encompass preventing or treating HIV infection, as disclosed in the specification and commensurate in scope with the claimed invention. In the absence of objective evidence commensurate in scope with the claimed methods, applicant has not provided convincing objective evidence that the claimed invention is effective as a therapeutic or preventative for HIV infection based on the in vitro inhibition of HIV infection of monocytes in vitro alone.

As pointed out previously; applicant's arguments of record have not been found persuasive and the rejection is maintained.

It has been noted that if applicant limits claims to the in vitro inhibition of HIV infection of mononuclear phagocytes or monocytes, then the rejection under 35 U.S.C. § 112, first paragraph would be withdrawn.

7. Claims 8 stands rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A) The previous rejection 35 U.S.C. 112, first paragraph, enablement with respect to the open language "comprising" and the scope of the claims reading on reverse transcriptase inhibitors as recited in claims 21-22 has been obviated by the cancellation of claims 21-22.
experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

B) Claim 8:

Applicant's arguments, filed 4/2/99 (Paper No. 49), have been fully considered but are not found convincing. Applicant simply asserts that the function description of the agent is entirely appropriate and that the method claims encomapss the use of agents not known at the time of filing, much less disclosed.

The following is reiterated for applicant's convenience.

With respect to agents that inhibit CD44-facilitated entry of HIV into cells sufficient to effect said inhibition other than CD44-specific antibodies/peptides and hyaluronic acid/hyaluronate; there is insufficient guidance and direction to agents commensurate with the enablement provided by the disclosure with regard to the large number of putative "agents" broadly encompassed by the claims. Further, the claims broadly encompass a significant number of inoperative species. It is not sufficient to define a specificity by its principal biological activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use of the claimed "agents" in manner reasonably correlated with the scope of the claims broadly including any number of "agents". Also, it is noted that minor structural differences even among structurally related compounds or compositions can result in substantially different pharmacological activities. The scope of the claims must bear a reasonable correlation with the scope of enablement. Without such guidance, the changes which can be made in the agent's structure and still maintain HIV inhibitory activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Applicant's arguments are not found persuasive.

8. The previous rejection under 35 U.S.C. § 112, first and second paragraphs, with respect to the recitation of "compounds, different from said anti-CD44 antibody, that blocks receptors for HIV infection on said mononuclear phagocyte" has been obviated by the cancellation of these claims.

9. Claim 11: It is apparent that the A1G3 antibody/hybridoma is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the hybridoma which produces this antibody. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

It is noted that the ATCC Catalog (8th Edition, 1994) discloses that the A1G3 (ATCC HB-177) antibody/hybridoma is available under the conditions that you will not use it for commercial purposes or distribute it to third parties. Therefore, the claimed antibody does not appear to be publicly available.

Biological materials must be known and readily available to the public (See MPEP 2404.01). Neither concept alone is sufficient. The fact that applicant and other members of the public were able to obtain the materials in question from a given depository prior to and after the filing date of the application does not establish the upon issuance of a patent on the application that such material would continue to be accessible to the public. The applicant did not make of record any of the facts and circumstances surrounding the access to the biological materials from the depository, nor is there any evidence as to the depository's policy regarding the material if a patent would be granted. Further, there is no assurance that the depository would allow unlimited access to the material if the application has matured into a patent. In the absence of evidence that the AG13 antibody/hybridoma is readily available to the public and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent.

Applicant's arguments, filed 4/2/99 (Paper No. 49), have been fully considered but are not found convincing for the reasons of record set forth in Paper No. 46. Applicant asserts that the antibodies are freely available and urges authority for the assertion that the catalog restriction is inconsistent with 35 USC 112, first paragraph.

Applicant is invited to review the previous paragraph of record.
Applicant's arguments are not found persuasive.

It is noted that requirement under 35 USC 112, first paragraph for the A3D8 antibody has been satisfied by its public/commercial availability, as evidenced by its availability from Sigma Chemical Company (see Catalog 1995, page 1171).

10. Claim 11 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Applicant amended claims, filed 4/2/99 (Paper No. 49) have obviated the previous rejection of claim 10 which lacked the recitation of the appropriate SEQ ID NOS.

B) Claim 11 stands indefinite in the recitation of "A1G3" because their characteristics are not known. The use of "A1G3" monoclonal antibodies as the sole means of identifying the claimed antibodies renders the claim indefinite because these terms are merely laboratory designations which do not clearly define the claimed products, since different laboratories may use the same laboratory designations to define completely distinct cell lines or hybridomas.
Applicant's arguments, filed 4/2/99 (Paper No. 49), have been fully considered but are not found convincing for the reasons of record set forth in Paper No. 46. Applicant believes no revision is necessary. Applicant is invited to recite the ATCC Accession No. to distinctly define the claimed antibody species.

C) The amendments must be supported by the specification so as not to add any new matter.

11. Claim 8, 9, 12 are rejected under 35 U.S.C. § 102(b) as being anticipated by Ueno et al. (U.S. Patent No. 4,840,941).

Applicant's arguments, filed 4/2/99 (Paper No. 49), have been fully considered but are not found convincing for the reasons of record set forth in Paper No. 46. Applicant simply asserts that the inherency is appropriate only when a particular result flows from the reference teachings, which is not supported by the examiner's comments.

Given the absence of objective evidence to the contrary; the teaching of Ueno et al. to use hyaluronic acid to inhibit retroviral and HIV infection (see entire document, particularly column 2, line 52; column 5, paragraph 2, Example 9) sets forth the substance of the invention. The claimed functional limitations addressed by the claimed methods would be inherent properties of the referenced hyaluronic acid/hyaluronate. Also, seeEx parte Novitski 26 USPQ 1389 (BPAI 1993).

Applicant's arguments are not found persuasive.

Applicant's arguments, filed 4/2/99 (Paper No. 49), have been fully considered but are not found convincing for the reasons of record set forth in Paper No. 46

12. Claims 8, 9 and 12 stand rejected under 35 U.S.C. § 103 as being unpatentable over Ueno et al. (U.S. Patent No. 4,840,941) in view of the art known use of AZT (zivodudine) to treat HIV infections at the time the invention was made.

Applicant's arguments, filed 4/2/99 (Paper No. 49), have been fully considered but are not found convincing for the reasons of record set forth in Paper No. 46

Given the absence of objective evidence to the contrary; the teaching of Ueno et al. to use hyaluronic acid to inhibit retroviral and HIV infection (see entire document, particularly column 2, line 52; column 5, paragraph 2, Example 9) sets forth the substance of the invention. Ueno et al. teaches the use of hyaluronic acid/hyaluronate in the treatment of HIV infections. It has been noted that Ueno et al. does not use the term "hyaluronate" per se but this pharmaceutical formulation would have known and readily apparent to the ordinary artisan at the time the invention was made, given the referenced teaching. This reference is silent about the use of reverse transcriptase inhibitors per se, even though it uses the reverse transcriptase assay. The use of AZT at the was known and used by the ordinary artisan at the time the invention was made to treat HIV infection. The motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose. Section MPEP 2144.07.

One of ordinary skill in the art at the time the invention was made would have been motivated to select the combination of hyaluronic acid/hyaluronate and reverse transcriptase inhibitor such as AZT to inhibit HIV infection under a number of in vitro, ex vivo and in vivo regimens. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments are not found persuasive.

13. It is noted that applicant has clearly stated that the instant invention is not drawn to the use of CD44-specific immunotoxins and that the current claimed recitation supports this conclusion.

14. No claim is allowed.

It has been noted that claims drawn to methods of inhibiting HIV infection of mononuclear phagocytes (versus a mixed cell population) in vitro with CD44-specific antibodies would be considered allowable.

15. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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09/753851

Application No.:_____

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☑ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other: _____

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☑ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). SEE SECTION 3 OF OFFICE ACTION

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

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